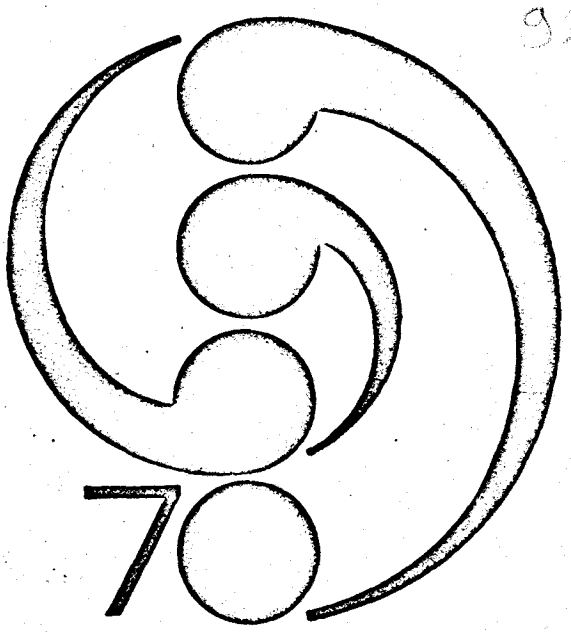
Genetics of Industrial Microorganisms



Abstract Book

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ABSTRACT BOOK

T9-1

Bacterial Wall Peptidoglycans; Mechanism of Action of Penicillins

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Bacterial wall peptidoglycans[1] are networks of glycan chains substituted by tetrapeptide units which, in turn, are crosslinked by peptide bridges. The glycan moiety is a chitin-like structure formed by linear strands of β-1,4 linked 2-acetamido-2-deoxy-D-glucose (N-acetylglucosamine) residues except, however, that every other sugar is substituted on C_3 by a D-lactyl group (N-acetylmuramic acid). The tetrapeptide units substitute through their N-termini the D-lactic acid groups of the glycan. They have the general structure L-alanyl (or L-seryl, or glycyl)-γ-D-glutamyl-L-R_3-D-alanine. The R_3 residue may be L-homoserine, L-diaminobutyric acid, L-ornithine, L-lysine, LL-diaminopimelic acid or meso-diaminopimelic acid. The crosslinking between the peptide units of adjacent glycan chains always extends from the C-terminal D-alanine of one peptide unit to an amino group of another unit. Depending upon the composition of the peptide bridges and the location of the amino group involved in the crosslinking, there appear four chemotypes of peptidoglycans[1].

The peptide crosslinking which follows the insertion of newly synthesized disaccharide peptide units into the growing wall peptidoglycan, is introduced by transpeptidation[2]. The peptide units which undergo transpeptidation are pentapeptides L-γ-D-glutamyl-L-R_3-D-alanyl-D-alanine either as such (peptidoglycans of chemotype I) or modified by prior addition to the ω- amino group of the L-R_3 residue or to the α-carboxyl group of D-glutamic acid, of those amino acid residues which in the completed wall peptidoglycan will serve as "specialized" peptide bridges. A membrane-bound transpeptidase catalyzes the transfer of the carboxyl group of the penultimate D-alanine

residue of one peptide donor to the amino group of a second peptide acceptor. Interpeptide bonds are formed and D-alanine residues are released in equivalent amounts. Many bacteria exhibit D-alanyl-D-alanine carboxypeptidase activities. The substrate requirements of the DD carboxypeptidases from Escherichia coli[3] and from Streptomyces albus G[4] and the substrate requirements of the membrane-bound transpeptidase present striking similarities, so that the DD carboxypeptidases appear to be uncoupled transpeptidases. A structural analogy between penicillins and the conformation of acyl-D-alanyl-D-alanine[5] accepted by the transpeptidase has been proposed to explain the molecular basis of the antibacterial action of penicillins and has been extented to explain the inhibiting effect exerted by these antibiotics upon the action of the E.coli DD carboxypeptidase. The isolation from the penicillins-resistant Streptomyces albus G of a DD carboxypeptidase which is not inhibited by penicillins seems to be at variance with this analogy hypothesis or, at least, it shows that this analogy is not universal among bacteria. The molecular basis for such a mechanism of penicillin resistance which does not involve the enzymatic degradation of the antibiotic, would reside in a peculiar structure of the transpeptidase (and of the carboxypeptidase) and would result from one or several mutations in the corresponding structural gene.

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